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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,506	07/31/2001	John G. Babish	T8638.NP	2768

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EXAMINER	
LEITH, PATRICIA A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,506	BABISH ET AL.	
	Examiner	Art Unit	
	Patricia Leith	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above claim(s) *21-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,43-57,63 and 64* is/are rejected.

7)☒ Claim(s) *16-20 and 58-62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-64 are pending in the application.

Claims 21-42 were withdrawn from examination on the merits as they are directed toward a non-elected invention without traverse in the response filed 6/27/04.

Claims 1-20 and 43-64 were examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office Action.

Claim Rejections - 35 USC § 112

Claims 1-15 and 43-47 remain rejected and claims 63 and 64 are newly rejected under 35 USC 112 first paragraph for lacking a written description of the scope of the invention.

Applicant argues, "the specification provides sufficient description and guidance for the claimed compositions" (Arguments, p. 13). Applicant quotes Gentech Inc v.

Novo Nordisk: "a specification need not disclose what is well known in the art" and contends that "the written description requirement for a claimed genus can be satisfied through sufficient description of a representative number of species".

However, it remains deemed that, although Applicant provided an example of a basic structure of a sesquiterpene lactone, and it is true that sesquiterpene lactones are known in the art, that Applicant has not provided an adequate 'representative' number of sesquiterpene lactones which would *function* commensurate in scope with the claimed invention.

Although Applicant has provided a simple backbone structure of a sesquiterpene lactone, it is noted that the functionality of the sesquiterpene lactone is not found in the backbone of these structures, but the functional groups *associated* with the sesquiterpene lactones. As it was keenly noted in the previous rejection under this statute, every sesquiterpene lactone is different in structure and function. Applicant has not provided a detailed description of a representative number of sesquiterpene lactones, i.e., not even 20 or 30 out of the thousands of sesquiterpene lactones known which would satisfy the functionality of the claimed composition which is to have COX-2 inhibitory activity, but to have minimal COX-1 activity. Being that the simple sesquiterpene lactone backbone (core structure) is not indicative of functionality, Applicant has failed to provide any *specific* structures of sesquiterpene lactones (besides parthenolide) which would function commensurate in scope with the claimed

invention. It is noted that all DNA provides for the same backbone structure, but it is well known that the backbone of DNA merely provides a support for different functioning units of amino acids which play the critical role in DNA function. Sesquiterpene lactones, numbering in the *thousands*, are similar to DNA or any other genus of chemical in that they provide the backbone structure for thousands upon thousands of respective functioning units that differ with respect to structure and reactivity. Thus, it remains standing that Applicant was not in possession of all sesquiterpene lactones in that a description which would indicate possession of at least a representative number of sesquiterpene lactones has not been sufficiently described in the Specification as originally filed.

Claims 1-15 and 43-57 remain rejected and claims 63-64 are newly rejected under 35 USC 112 first paragraph for the reasons set forth in the previous Office Action.

Applicant argues, "Applicant's representative is not aware of the precedent for such an assertion with respect to human therapy and would appreciate being provided with the relevant authority so that the case law can be reviewed and responded to appropriately". (p.14- Arguments). The Examiner does not know what Applicant means by 'relevant authority' and exactly what Applicant would like the Examiner to provide. However, the paragraph in the previous Office Action; "inventions.....unpredictability in biological responses to therapeutic treatments" is a general statement regarding the state of the art. Applicant argues that "the billions of dollars earned by the

pharmaceutical industry belies the assertion in the Office Action that effective treatments for disease conditions are relatively rare and are therefor unbelievable". First, the paragraph stated by the Office Action states 'may be unbelievable" and not "are therefore unbelievable". Further, treatments for diseases *are* rare. Take for example cancer, AIDS, Alzheimer's, rheumatoid arthritis, crone's disease, influenza, tuberculosis and common cold to name a few. All of these diseases are difficult to treat, and *effective* treatments are rare. 'The billions of dollars earned by the pharmaceutical industry' does not afford relevance to the rarity of treatments for these diseases. If treatments for these diseases as well as others were abundant, then perhaps the pharmaceutical industries would be earning less money. Nonetheless, the argument is superfluous to the outstanding rejection.

Applicant argues, "the claimed compositions contain sesquiterpene lactones that share structural and functional characteristics in that they have the structure of sesquiterpene lactones and function to inhibit inducible COX-2 activity and have minimal effect on COX-1 activity" (p. 14, Arguments). However, as it was discussed *supra* in the Written Description rejection, all sesquiterpene lactones do not share such a similar structure that they would be expected to display similar affectivity *in-vivo*. On the contrary, as evidenced by Quintero et al. who studies seven sesquiterpene lactones on HeLa cell proliferation, only two of the sesquiterpene lactones, derived from the same plant material, actually provided for any beneficial effects (see entire document, especially Figure 2). Similarly, Foglio et al. found that only one of two sesquiterpene

lactones extracted from *Artemisia annua* provided for antiulcerogenic activity (see Abstract). Thus provides indication that sesquiterpene lactones, although sharing the same underlying backbone structure, provide for different effects when administered *in-vivo* due to the grave differences in their respective functional groups.

Applicant argues that "based on the teachings and in the specification and what was well known in the art, one skilled in the art would expect that the claimed compositions, which are directed to compositions having specifically recited characteristics of inhibiting COX-2 activity and having minimal effect on COX-1 activity, to function as claimed (p. 15, Arguments). Applicant refers to a reference by Hwang et al. to support their contentions.

However, the reference by Huang et al. seems to support the Instant *rejection* for the following reasons: Huang et al., although impervious to the exact mechanism of action of the effective sesquiterpene lactones on COX-2 inhibition, did agree that that "it appears to be a general feature that many PTK inhibitors derived from natural products possess functional moieties that can confer conjugate addition reaction with biological nucleophiles such as SH group. Compounds 6, 8 and 9 lack the epoxide, and their inhibitory activity was diminished as compared with parthenolide....compounds 11 and 12 containing an epoxide moiety without alpha-methylene-gamma-lactone moiety showed loss of the inhibitory activity" (p.816). This supports the Instant rejection in that it shows that all sesquiterpene lactones are not equal in structure or function. It also

demonstrates that some sesquiterpene lactones, approximately 50% of those tested had no inhibitory activity thus raising the level of unpredictability of the functionality of all or even a representative number of sesquiterpene lactones on COX-2 inhibition.

Although most of the discussion has been concerned with sesquiterpene lactones, it is the opinion of the Examiner that the basic principal concerning lack of written description also holds true with diterpene lactones and triterpene lactones as discussed in the previous Office Action. The Specification does not provide for any other diterpene lactones or triterpene lactones besides andrographolide and ursolic acid or oleanic acid which has provided for the claimed effects.

The unpredictability of sesquiterpene lactones as a genus, as well as the lack of guidance within the Instant specification of which sesquiterpene lactones, triterpene lactones and diterpene lactones will function in a manner commensurate in scope with the claimed invention, would preclude the skilled artisan from making and using the breath of the claimed invention. The skilled artisan would have a reasonable expectation that a number, perhaps 50% or more of sesquiterpene lactones *would not* function as stated by the Instant claims especially in light of the knowledge of the state of the art. However, the affectivity of each sesquiterpene lactone, triterpene lactones and diterpene lactones would need to be tried and tested on their own accord. Due to the *thousands* of these lactones being known in the art, testing of each compound

would be rigorous, tedious, time consuming and expensive thus constituting undue experimentation.

Claims 16-20 and 58-62 remain objected to for the reasons set forth in the previous Office Action.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patricia Leith
Primary Examiner
Art Unit 1654

11/29/04